Journal of Intensive Medicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Journal of Intensive Medicine

journal homepage: www.elsevier.com/locate/jointm

Review

Cytokine storm in acute respiratory distress syndrome

Raffaele Merola[1], Patricia R.M. Rocco[2], Vito Marco Ranieri[3,4], Denise Battaglini[5,6,*]

[1] *Anesthesia and Intensive Care Medicine, Department of Neurosciences, Reproductive and Odontostomatological Sciences, University of Naples Federico II, Naples, Italy*
[2] *Laboratory of Pulmonary Investigation, Carlos Chagas Filho Institute of Biophysics, Federal University of Rio de Janeiro, Avenida Carlos Chagas Filho, s/n, Bloco G-014, Ilha do Fundão, Rio de Janeiro, Brazil*
[3] *Department of Precision and Regenerative Medicine and Ionian Area (DiMePRe-J) Research Departments, University Aldo Moro, Bari, Italy*
[4] *Anesthesia and Intensive Care Medicine, Policlinico di Bari, Bari, Italy*
[5] *Department of Surgical Sciences and Integrated Diagnostics (DISC), University of Genoa, Genova, Italy*
[6] *Anesthesia and Intensive Care, IRCCS Ospedale Policlinico San Martino, Genova, Italy*

ARTICLE INFO

Managing Editor: Jingling Bao/Zhiyu Wang

Keywords:
Acute respiratory distress syndrome (ARDS)
Cytokines
"Cytokine storm"
Multiorgan dysfunction syndrome (MODS)
Subphenotypes

ABSTRACT

Acute respiratory distress syndrome (ARDS) is a life-threatening condition characterized by diffuse acute inflammatory lung injury, non-cardiogenic pulmonary edema, and severe hypoxemia. Beyond structural damage, ARDS reflects a profound dysregulation of both innate and adaptive immune responses. Uncontrolled activation of inflammatory pathways disrupts the alveolar–capillary barrier and amplifies cytokine release, which may disseminate systemically as a "cytokine storm." This maladaptive immune response worsens pulmonary injury and contributes to the development of multiorgan dysfunction syndrome (MODS), the leading cause of death in ARDS. This review summarizes current understanding of the cellular and molecular mechanisms underlying "cytokine storm," with emphasis on its systemic effects and its relationship to ARDS subphenotypes, particularly the hyperinflammatory subphenotype, characterized by distinct biomarker profiles, differential treatment responses, and worse outcomes. We also discuss clinical implications and therapeutic strategies, ranging from established interventions such as lung-protective ventilation and corticosteroids to emerging immunomodulatory approaches, including inhibition of interleukin (IL)-1 and IL-6 signaling, extracorporeal cytokine removal, cytokine nanosponges, as well as mesenchymal stromal cell (MSC) and MSC-derived extracellular vesicle therapies. Finally, we emphasize the potential of precision medicine, in which biomarker-guided strategies may allow early identification of patients at risk for a cytokine storm and support the selection of targeted therapies. By aligning treatment with individual inflammatory profiles, these approaches aim to limit immune-mediated organ injury and improve clinical outcomes in ARDS, thereby linking mechanistic insights to patient-centered care.

Background

Acute respiratory distress syndrome (ARDS) is a life-threatening form of hypoxemic respiratory failure, characterized by bilateral pulmonary infiltrates not fully explained by fluid overload or cardiac dysfunction.[1] ARDS can result from direct pulmonary insults, including pneumonia, aspiration, or inhalational injury, or from indirect, extrapulmonary triggers encompassing sepsis, trauma, and severe burns.[2] The primary site of injury differs by etiology: alveolar epithelial damage predominates in direct ARDS, whereas capillary endothelial injury is typical of indirect ARDS.[3] Regardless of the etiology, the disruption of the alveolar–capillary barrier increases vascular permeability, leading to protein-rich pulmonary edema, alveolar collapse, impaired gas exchange, hypoxemia, and often hypercapnia.[4]

Beyond the lungs, ARDS triggers systemic consequences. Activation of innate immune cells, including macrophages and dendritic cells, initiates a dysregulated inflammatory cascade marked by cytokine release and neutrophil recruitment.[5] This response not only worsens lung injury but can propagate systemically, driving multiple organ dysfunction syndrome (MODS), the leading cause of death in ARDS.[6–8] In this context, the lung functions not as a target organ but also as a source and amplifier of systemic inflammation.[9]

The coronavirus disease 2019 (COVID-19) pandemic highlighted the dual role of host immunity: essential for pathogen clearance, yet potentially catastrophic when dysregulated.[10]

* Corresponding author: Denise Battaglini, Department of Surgical Sciences and Integrated Diagnostics (DISC), University of Genoa, Genova, 16132, Italy.
E-mail address: denise.battaglini@unige.it (D. Battaglini).

https://doi.org/10.1016/j.jointm.2025.12.001
Received 21 October 2025; Received in revised form 25 November 2025; Accepted 2 December 2025
Available online xxx
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Please cite this article as: R. Merola, P.R.M. Rocco, V.M. Ranieri et al., Cytokine storm in acute respiratory distress syndrome, Journal of Intensive Medicine, https://doi.org/10.1016/j.jointm.2025.12.001

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The concept of a "cytokine storm," first described in the setting of acute graft-*vs.*-host disease, has long been recognized as a central contributor to multiorgan injury in ARDS.[11,12]

This review aims to integrate current knowledge on the role of "cytokine storm" in ARDS pathophysiology, its contribution to MODS, and the resulting clinical implications. We also discuss therapeutic strategies to mitigate immune-mediated injury, from established supportive interventions such as lung-protective ventilation and corticosteroids to emerging immunomodulatory approaches, highlighting the potential of biomarker-guided precision medicine to improve patient outcomes.

Pathophysiological Features of "Cytokine Storm" in ARDS

The inflammatory response in ARDS involves multiple immune and structural cells, as illustrated in (Figure 1). Inflammation is a natural biological process designed to eliminate pathogens and promote tissue repair through coordinated activation of the innate and adaptive immune systems.[13] Under normal conditions, the immune response is proportional to the threat and resolves once the pathogen is cleared. Cytokines, small signaling proteins, play a central role in this process by directing immune cell activity while limiting tissue damage. Their effects are generally local and transient, restricted to the site of infection or injury.[12,13]

In ARDS, these regulatory mechanisms may fail. Excessive immune activation results in overproduction of pro-inflammatory cytokines and soluble mediators, leading to "cytokine storm." Once these mediators enter the systemic circulation, they trigger widespread inflammation, tissue injury, and MODS.[12,14] The alveolar–capillary barrier is particularly susceptible; neutrophil infiltration, oxidative stress, and cytokine-mediated injury compromise barrier integrity, causing alveolar flooding, impaired gas exchange, and progressive respiratory failure.[15] Severe infections, such as Severe Acute Respiratory

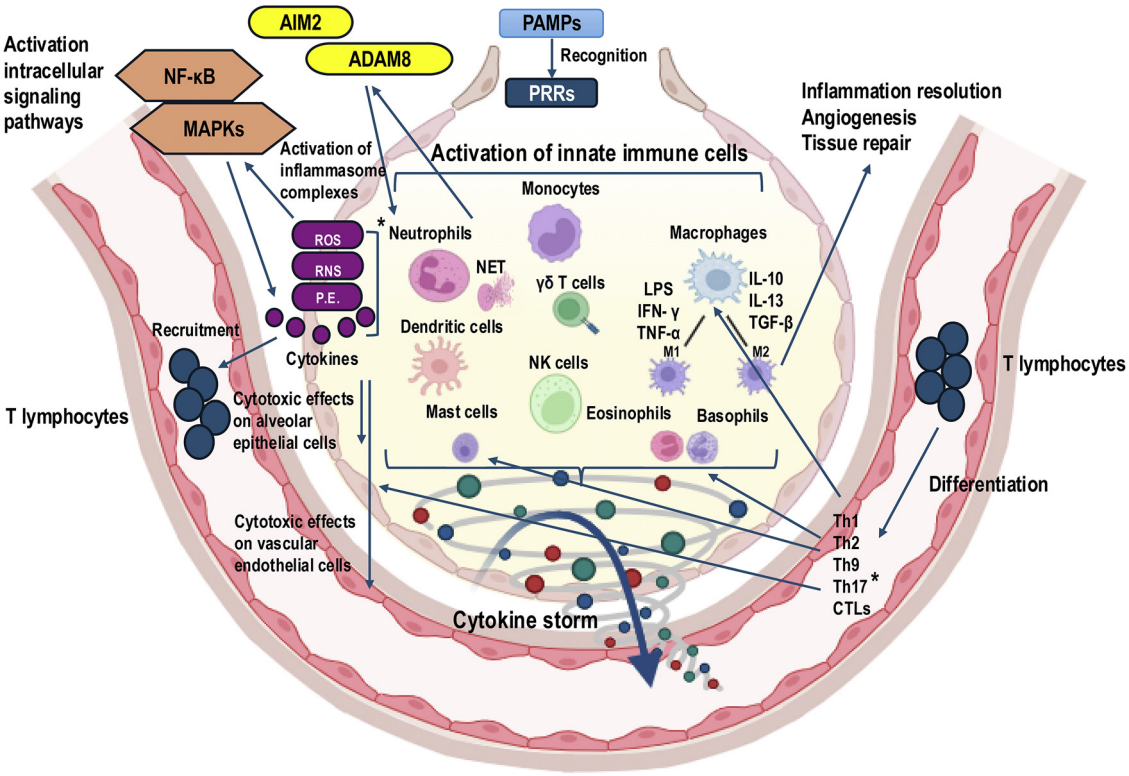

Figure 1. Innate and adaptive immune cells driving the cytokine storm in ARDS. The innate immune system constitutes the first line of defense against pathogens, relying on neutrophils, monocytes, macrophages, dendritic cells, $\gamma\delta$ T cells, and NK cells. These cells recognize PAMPs through germline-encoded PRRs, initiating signaling cascades that trigger cytokine and chemokine secretion. This rapid response restricts infection and bridges innate and adaptive immunity by recruiting lymphocytes. In cytokine storm, neutrophils, macrophages, and NK cells are key mediators. During early ARDS, neutrophils accumulate in alveoli and the lung interstitium, releasing ROS, RNS, proteolytic enzymes, and pro-inflammatory cytokines. These factors damage alveolar epithelial and endothelial cells, disrupt the alveolar-capillary barrier, and increase vascular permeability. Oxidative stress further amplifies inflammation via NF-κB and MAPK signaling pathways and promotes effector T lymphocyte recruitment, contributing to multiorgan dysfunction. NETs – composed of chromatin, histones, and antimicrobial proteins – help control pathogens but, in excess, activate inflammasomes such as AIM2 and molecules including ADAM8, stimulating macrophages and cytokine release, thereby exacerbating lung injury. Macrophages, normally involved in clearance, tissue repair, and antigen presentation, may become hyperactivated, releasing large amounts of cytokines. Depending on stimuli, they polarize into M1 (pro-inflammatory; induced by LPS, TNF-α, IFN-γ) or M2 (anti-inflammatory; induced by IL-10, IL-13, TGF-β) subphenotypes. NK cells, in contrast, often exhibit impaired cytolytic activity during cytokine storms, limiting the clearance of infected or dysregulated cells. Adaptive T lymphocytes also contribute: Th1 and cytotoxic T lymphocytes promote antiviral responses and macrophage activation, whereas Th2, Th9, and Th17 subsets recruit eosinophils, basophils, mast cells, and neutrophils, amplifying inflammation. The interplay of these innate and adaptive immune cells drives excessive cytokine release, tissue damage, alveolar-capillary barrier disruption, and multiorgan dysfunction in ARDS.
AIM2: Absent in Melanoma 2; ADAM8: A Disintegrin and metalloproteinase domain-containing protein 8; ARDS: Acute respiratory distress syndrome; CTL: Cytotoxic T lymphocytes; IFN: Interferon; IL: Interleukin; LPS: Lipopolysaccharide; MAPK: Mitogen-activated protein kinase; NETs: Neutrophil extracellular traps; NF-κB: Nuclear factor-kappab; NK: Natural killer; PAMP: Pathogen-associated molecular patterns; P.E.: Proteolytic enzymes; PRR: Pattern recognition receptors; RNS: Reactive nitrogen species; ROS: Reactive oxygen species; TGF: Transforming growth factor; Th: T helper cells; TNF: Tumor necrosis factor.

Table 1
The main pro-inflammatory cytokines in ARDS.

Pro-inflammatory cytokine	Source	Biological effects and clinical implications in ARDS
TNF-α	Macrophages, monocytes, neutrophils	Increases vascular permeability leading to pulmonary edema Upregulates endothelial adhesion molecules (ICAM-1, VCAM-1) promoting leukocyte recruitment; Activates NF-κB and MAPK pathways amplifying IL-1β, IL-6, and IL-8 production Elevated sTNFr-1 in hyperinflammatory ARDS subphenotype Anti-TNF therapies have been investigated but are limited by infection risk.
IL-1β	Macrophages	Induces IL-8 and MCP synthesis, enhancing leukocyte trafficking and edema Downregulates VE-cadherin, impairing endothelial barrier integrity High levels inversely correlated with survival in ARDS
IL-6	Mononuclear phagocytes, Endothelial cells	Drives inflammation via JAK2/STAT3 pathway Key mediator in COVID-19 cytokine storm with levels correlating with severity and mortality Elevated in hyperinflammatory ARDS subphenotype
IL-33	Epithelial cells	Nuclear alarmin released upon injury Activates macrophages via STAT3 → MMP2/9 release → ECM damage Elevated in serum, BALF, and lung tissue during early ARDS Experimental modulation attenuates lung inflammation by regulating Th17/Treg balance and autophagy
HMGB1	Necrotic cells, Neutrophils, Macrophages	Late-phase mediator released passively or actively Prognostic biomarker for ARDS and mortality in experimental models Regulates dendritic cell function through PI3K/Akt/mTOR signaling Pharmacologic inhibition improves outcomes in preclinical ARDS and sepsis
IFN-γ	Activated T lymphocytes, NK cells	Enhances macrophage activation Upregulates MHC I/II Strengthens antigen presentation Amplifying adaptive immunity
GM-CSF	T lymphocytes, NK cells, Epithelial cells, Macrophages	Promotes survival and activation of neutrophils and macrophages Amplifying inflammatory injury in the lung

ARDS: Acute respiratory distress syndrome; Akt: Protein kinase B; BALF: Bronchoalveolar lavage fluid; COVID-19: Coronavirus disease 2019; ECM: Extracellular matrix; GM-CSF: Granulocyte-macrophage colony-stimulating factor; HMGB1: High mobility group box1; ICAM-1: Intercellular adhesion molecule 1; IFN: Interferon; IL: Interleukin; JAK2: Janus kinase 2; LCA: Latent class analysis; MAPK: Mitogen-activated protein kinase; MCPs: Monocyte chemoattractant proteins; MHC: Major histocompatibility complex; MMP2: Matrix metalloproteinase-2; MMP9: Matrix metalloproteinase-9; mTOR: Mammalian target of rapamycin; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells; NK:Natural killer cells; PI3K: Phosphatidylinositol 3′-kinase; sTNFr-1: Soluble tumor necrosis factor receptor-1; STAT3: Signal transducer and activator of transcription 3; Th,:T helper cells; TNF: Tumor necrosis factor; Treg: Regulatory T cells; VCAM-1: Vascular cell adhesion molecule 1; VE-cadherin: Vascular endothelial cadherin.

Syndrome Coronavirus 2 (SARS-CoV-2), illustrate this exaggerated immune response.[16]

Notably, ARDS is a heterogeneous syndrome with distinct biological subphenotypes, particularly the hyperinflammatory and hypoinflammatory subphenotypes, which differ markedly in clinical features, biomarker profiles, immune responses, and outcomes.[17–22] The hyperinflammatory subphenotype is characterized by elevated levels of pro-inflammatory cytokines (e.g., interleukin [IL]−6, IL-8, soluble tumor necrosis factor receptor-1 [sTNFr-1]), and markers of endothelial cell damage, thereby leading to more severe shock, metabolic acidosis, and worse clinical outcomes. In contrast, the hypoinflammatory subphenotype exhibits lower cytokine levels, milder organ dysfunction, and better outcomes. These subphenotypes also differ according to their responses to ventilatory strategies (e.g., positive end-expiratory pressure [PEEP]), fluid management, and pharmacological treatment, underscoring the potential for subphenotype-guided treatment.[17–22] In COVID-19-related ARDS, most patients display the hyperinflammatory subphenotype, consistent with the severe cytokine-mediated pathology.[23]

In summary, the “cytokine storm” in ARDS reflects an exaggerated and dysregulated immune response with systemic consequences, highlighting the importance of recognizing biological subphenotypes to guide personalized treatment strategies.[24,25]

Cytokines are central to the pathogenesis of ARDS, orchestrating and amplifying the complex inflammatory cascade that drives this syndrome.[7] Their production is triggered by the recognition of danger- and pathogen-associated molecular patterns (DAMPs and PAMPs) through pattern recognition receptors (PRRs), including Toll-like receptors (TLRs), expressed by alveolar macrophages, epithelial cells, and other immune effectors.[26] The subsequent activation of transcription factors such as nuclear factor-kappaB (NF-κB) and activating protein-1 triggers the release of a broad array of cytokines and chemokines that orchestrate both local and systemic inflammation.[27]

When produced in excess, these mediators drive uncontrolled systemic inflammation, which contributes to tissue injury and secondary organ dysfunction.[28] Elevated levels of pro-inflammatory cytokines IL-6, IL-8, and tumor necrosis factor (TNF) sustain the inflammatory cascade, recruiting and activating neutrophils and macrophages, which release reactive oxygen species, proteases, and lipid mediators, such as prostaglandins and leukotrienes.[12,29] These substances exacerbate tissue damage, particularly at the alveolar epithelium and capillary endothelium, compromising the integrity of the alveolar-capillary barrier.[30] The resulting increase in vascular permeability leads to alveolar flooding, impaired gas diffusion, ventilation-perfusion mismatch, and hypoxemia, hallmarks of ARDS[31] Tables 1, 2, and 3 summarize the key inflammatory cytokines, anti-inflammatory cytokines, and chemokines involved in ARDS, their biological effects, and clinical implications, providing a framework for potential therapeutic interventions.

Mechanism of Organ dDmage in “Cytokine Storm”

The lung, the primary site where the cytokine storm originates in ARDS, is also one of its principal targets. Its pathophysiological alterations have been comprehensively described in the preceding section and are therefore not repeated here. The release of cytokines from the lung to the systemic circulation represents the *primum movens* of MODS. In fact, once dissemi-

Table 2
The main anti-inflammatory cytokines in ARDS.

Anti-inflammatory cytokine	Source	Biological effects and clinical implications in ARDS
IL-1RA	Monocytes, macrophages	Natural inhibitor of IL-1β signaling Upregulated in ARDS Paradoxically, elevated IL-1RA levels associated with adverse outcomes in pediatric ARDS
IL-10	Macrophages, Treg cells	Suppresses excessive inflammation Maintains immune homeostasis and limits tissue injury In murine sepsis-induced lung injury, increased IL-10 expression markedly reduced lung damage
IL-13	Innate lymphoid cells Treg cells	Regulates tissue repair, fibrosis, and resolution of inflammation Promotes reparative macrophage polarization Enhances alveolar epithelial regeneration IL-13-deficient mice show greater susceptibility to lung injury and higher mortality
IL-22	Innate lymphoid cells T helper cells	Acts on epithelial (not immune) cells Promotes epithelial repair and barrier integrity Reduces pulmonary leakage and susceptibility to bacterial superinfection (e.g., post-influenza ARDS) In LPS-induced ARDS models, IL-22: Fc reduced inflammation, preserved endothelial glycocalyx, and boosted endogenous IL-22 production

ARDS: Acute respiratory distress syndrome; Fc: Fragment crystallizable; IL: Interleukin; Treg cells: Regulatory T cells; LPS: Lipopolysaccharide; RA: Receptor antagonist.

Table 3
Principal chemokines implicated in the ARDS cytokine storm.

Chemokine	Source	Biological effects and clinical implications in ARDS
IL-8	Neutrophils, fibroblasts, epithelial cells, endothelial cells, hepatocytes, alveolar macrophages	Potent neutrophil chemoattractant and activator Predominantly secreted by alveolar macrophages and epithelial cells in response to DAMPs and PAMPs Elevated levels in BALF and pulmonary edema fluid strongly correlate with mortality, especially in sepsis-induced ARDS Pathological effects mediated via CXCR1/CXCR2 axis, driving excessive neutrophil infiltration and lung injury Identified as significantly higher in the hyperinflammatory subphenotype by latent class analysis
CXCL12	Monocytes, macrophages, lymphocytes, platelets	Regulates immune cell differentiation, polarization, and tissue regeneration Promotes epithelial cell survival and reduces apoptosis, with potential cytoprotective effects Under persistent inflammation, dysregulated expression promotes fibroblast activation and pulmonary fibrosis, impairing recovery
CXCL 10	Monocytes, macrophages, lymphocytes, platelets	Modulates adaptive immunity by influencing Th1/Th2 balance Regulates macrophage polarization toward M1 (pro-inflammatory) or M2 (reparative) phenotypes Dual role in amplifying tissue injury or promoting repair depending on inflammatory context
CCL5	Monocytes, macrophages, lymphocytes, platelets	Modulates adaptive immune responses in ARDS Influences T-helper cell polarization and the Th1/Th2 balance Contributes to leukocyte recruitment and sustained lung inflammation

ARDS: Acute respiratory distress syndrome; BALF: Bronchoalveolar lavage fluid; CCL: C–C motif ligand; CXCL: C-X-C motif chemokine ligand; CXCR: C-X-C motif chemokine receptor; DAMPs: Danger-associated molecular patterns; IL: Interleukin; PAMPs: Pathogen-associated molecular patterns; Th: T helper cells.

nated, circulating cytokines are potentially capable of causing deleterious effects on all organ systems (Figure 2).

Central nervous system

In the central nervous system, “cytokine storm” can precipitate a cascade of pathological events, including vascular leakage, activation of the complement system, and coagulation abnormalities, predisposing to cerebrovascular events such as stroke and ischemic necrosis.[32] Endothelial injury of cerebral vessels compromises the blood–brain barrier (BBB), allowing cytokines to penetrate brain parenchyma and initiate neuroinflammation.[33] Activated microglia and astrocytes amplify this response by releasing additional pro-inflammatory mediators, leading to neuronal injury and neurodegeneration.[34,35]

Cardiovascular system

In the myocardium, cytokines increase vascular permeability, leading to interstitial edema, impair cardiac contractility and may culminate in cardiogenic shock and multiple organ failure due to inadequate tissue perfusion.[36] Notably, IL-1 exerts a pronounced negative inotropic effect by disrupting mitochondrial function, reducing energy production, and increasing reactive oxygen species (ROS) generation, ultimately promoting cardiomyocyte death.[37] The subsequent release of intracellular autoantigens sustains inflammation,[38] while cytokine-induced electrophysiological instability promotes arrhythmias such as atrial fibrillation, tachycardia, bradycardia, and refractory ventricular fibrillation.[39] These pathophysiological alterations are compounded by heart-lung interactions, particularly during mechanical ventilation, where elevated intrathoracic pressure reduces venous return and right ventricular preload,[40] worsening right heart dysfunction in severe ARDS.[41,42]

Bone marrow

Cytokines profoundly disrupt hematopoiesis by directly impairing hematopoietic stem cell self-renewal and differentiation, while simultaneously damaging the bone marrow microenvironment. Prolonged exposure to pro-inflammatory cytokines, such as TNF-α, interferon (IFN)-γ, and IL-6 accelerates cellular senescence, depletes stem cell pools, and irreversibly injures stromal cells, leading to anemia, leukopenia, and thrombocytopenia.[43–45]

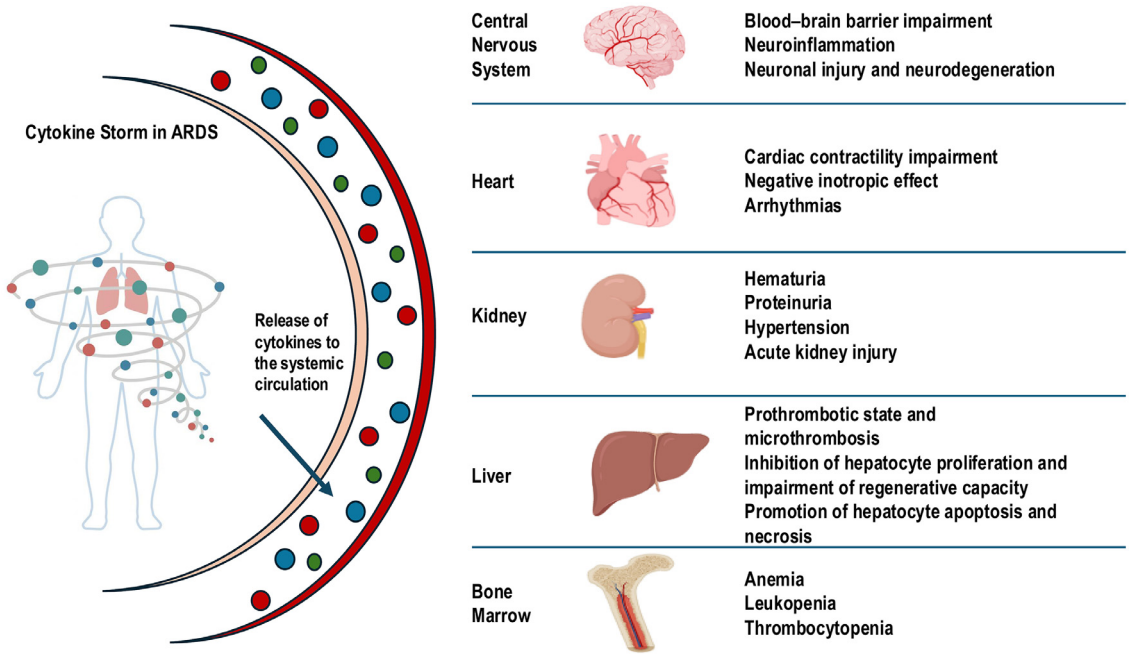

Figure 2. Multiorgan involvement in the ARDS cytokine storm. The uncontrolled release of pro-inflammatory cytokines from the injured lung into the systemic circulation initiates a cascade of multisystem damage. In the central nervous system, cytokine-mediated endothelial dysfunction compromises the blood–brain barrier, facilitating the entry of circulating mediators into the parenchyma. This leads to microglial and astrocytic activation, amplification of neuroinflammatory pathways, coagulation abnormalities, and enhanced susceptibility to ischemic injury and neuronal degeneration. In the heart, cytokines increase vascular permeability and disrupt mitochondrial oxidative phosphorylation. These alterations impair myocardial contractility, promote interstitial edema, and create an electrophysiological substrate for arrhythmias ranging from tachyarrhythmias to refractory ventricular fibrillation. The bone marrow is affected through cytokine-mediated suppression of hematopoietic stem cell renewal and stromal injury, leading to multilineage cytopenias. In the kidney, sustained inflammatory signaling produces vascular dysregulation and tubular stress, driven by endothelial injury, immune-cell infiltration, and cytokine-induced alterations in intrarenal hemodynamics. These changes impair glomerular filtration and tubular function, manifesting clinically as proteinuria, hematuria, and progression to acute kidney injury. In the liver, inflammatory cytokines stimulate acute-phase protein synthesis, activate complement and coagulation pathways, and foster a prothrombotic microenvironment. Furthermore, by activating intracellular signaling pathways, they inhibit hepatocyte proliferation, compromising their regenerative capacity, and promote apoptosis and necrosis. Collectively, these systemic effects converge to drive the progression from localized lung injury to widespread multiorgan dysfunction.
ARDS: Acute respiratory distress syndrome.

Renal function

Renal involvement manifests as hematuria, proteinuria, and acute kidney injury (AKI) progressing to renal failure.[46] Pathogenic mechanisms encompass immune cell infiltration, microthrombosis, and impaired renal perfusion. IL-6-driven Th-17 differentiation promotes the release of IL-17 and TNF-α, reducing endothelial nitric oxide (NO) bioavailability in vascular endothelium, promoting vasoconstriction and ischemia.[47,48] In parallel, IFN-γ upregulates the expression of intrarenal angiotensinogen, activating the renin-angiotensin-aldosterone system (RAAS), which contributes to hypertension, glomerulosclerosis, and fibrosis.[49,50] Systemic factors, including reduced cardiac output, hypoxemia, and hepatic dysfunction (i.e., hepatorenal syndrome), exacerbate renal injury.[51,52]

Liver

Cytokine-induced hepatotoxicity is mediated by IL-1, IL-6, TNF-α, and IFN-γ.[53] IL-6 binds to its receptor (IL-6R) to stimulate the hepatic synthesis of acute-phase proteins (e.g., C-reactive protein [CRP]), serum amyloid A, and fibronectin, which activate complement and coagulation cascades, fostering a prothrombotic state and microthrombosis,[54] which can evolve into disseminated intravascular coagulation (DIC).[55] The liver contains a large population of natural killer cells, which, when excessively activated, trigger the IFN-γ–signal transducer and activator of transcription 1 (STAT1) signaling pathway, thereby inhibiting hepatocyte proliferation and impairing regenerative capacity.[56] Finally, elevated TNF-α levels activate the ROS- c-Jun N-terminal kinase signaling cascade, promoting hepatocyte apoptosis and necrosis.[57]

Clinical Implications of "Cytokine Storm"

ARDS exhibits substantial biological heterogeneity,[58,59] particularly in inflammatory and injury-related biomarkers. Latent class analysis (LCA) of clinical and biomarker data from multiple randomized controlled trials (RCTs) has identified two reproducible ARDS subphenotypes: hyperinflammatory and hypoinflammatory.[17] The hyperinflammatory subphenotype is characterized by markedly elevated plasma concentrations of inflammatory mediators, higher vasopressor requirements, lower serum bicarbonate levels, and a greater prevalence of sepsis. Clinically, patients with this profile experience higher mortality, fewer ventilator-free days, and fewer organ failure-free days compared with the hypoinflammatory group (Figure 3).[17]

These subphenotypes can be reliably identified using a limited set of clinical and biomarker variables, and they exhibit

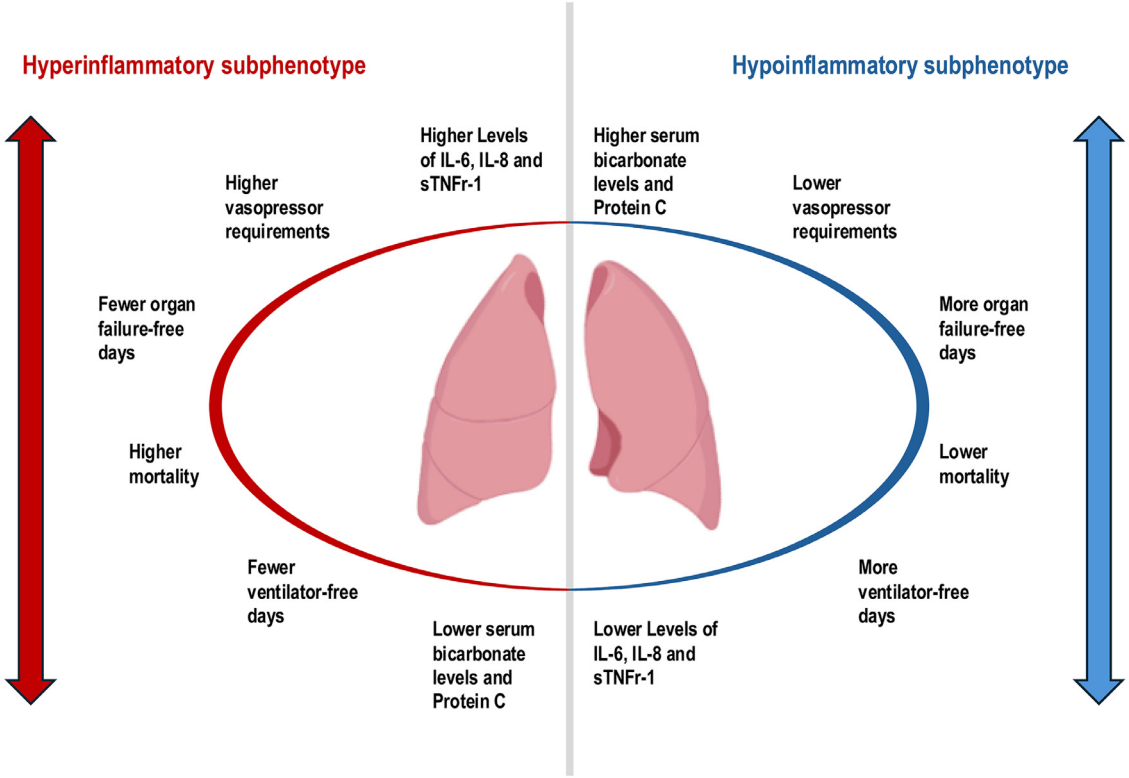
Hyperinflammatory subphenotype
Hypoinflammatory subphenotype
Higher Levels of IL-6, IL-8 and sTNFr-1
Higher vasopressor requirements
Higher serum bicarbonate levels and Protein C
Lower vasopressor requirements
Fewer organ failure-free days
More organ failure-free days
Higher mortality
Lower mortality
Fewer ventilator-free days
More ventilator-free days
Lower serum bicarbonate levels and Protein C
Lower Levels of IL-6, IL-8 and sTNFr-1

Figure 3. Biomarkers and outcomes of the acute respiratory distress syndrome subphenotypes. The hyperinflammatory subphenotype is characterized by elevated plasma levels of inflammatory mediators and lower serum bicarbonate and Protein C levels. Clinically, patients with this profile experience greater vasopressor requirements, higher mortality, fewer ventilator-free days, and fewer organ failure-free days compared with the hypoinflammatory subphenotype, reflecting the substantial biological heterogeneity in acute respiratory distress syndrome.
IL: Interleukin; sTNFr-1: Soluble tumor necrosis factor receptor-1.

differential responses to interventions, including fluid management strategies.[18] Furthermore, cluster analysis of a broad panel of 20 biomarkers encompassing inflammation, coagulation, and endothelial activation has identified two phenotypes: "reactive" and "uninflamed.[22]" The reactive subphenotype is defined by elevated levels of IL-6, IFN-γ, angiopoietin-1/2, and plasminogen activator inhibitor-1, and is associated with increased ICU mortality, highlighting the prognostic significance of systemic cytokine activation.[22]

While inflammatory biomarkers alone may be non-specific[60]; integrated biomarker panels reflecting endothelial injury (e.g., angiopoietin-2, intracellular adhesion molecule-1), epithelial damage (e.g., soluble receptor for advanced glycation end-products, surfactant protein-D), systemic inflammation (e.g., IL-6, IL-8, TNF-α), and dysregulated coagulation (e.g., protein C, plasminogen activator inhibitor-1, fibrinogen, D-dimer) reliably distinguish biologically meaningful subphenotypes. These distinctions help explain the variable efficacy of certain pharmacological therapies in unselected ARDS populations.[61,62] Indeed, subphenotypic stratification consistently correlates with differences in treatment responses and clinical outcomes.[18,21]

Identification of the hyperinflammatory subphenotype, marked by elevated IL-6, IL-8, and sTNFr-1, has several clinical implications. It enables refined prognostication by identifying patients at the highest risk of poor outcomes, provides a rationale for targeted immunomodulatory therapies, and informs clinical trial design to improve the detection of treatment effects. A detailed understanding of the cytokine milieu in ARDS thus underpins patient stratification, risk prediction, and the development of precision therapies.[31]

Therapeutic Perspectives

The clinical management of ARDS remains largely supportive, with mechanical ventilation as the cornerstone of therapy. Lung-protective strategies, using low tidal volumes (4–6 mL/kg predicted body weight), limited plateau pressures (<30 cmH_2O) and driving pressure (<14 cmH_2O), and adequate fluid balance, have been shown to mitigate ventilator-induced lung injury (VILI) and improve survival.[63,64] Moreover, PEEP should be individualized.[25] These approaches also reduce both local and systemic cytokine levels in preclinical[65] and clinical[66] studies.

Beyond ventilatory management and supportive care aimed at preserving vital organ function, the treatment of "cytokine storm" in ARDS involves immunosuppressive and immunomodulatory therapies to curb the detrimental effects of immune dysregulation.[12,67]

Corticosteroids remain a central therapeutic option, although their role has been debated.[68] Experimental studies demonstrate that corticosteroids suppress lung expression of TNF-α, IL-1β, and IL-6, while reducing neutrophil-derived ROS and attenuating tissue injury.[69,70] Clinically, prolonged methylprednisolone therapy improved lung injury and MODS scores and reduced mortality in ARDS[71] and a short course of low-dose cor-

ticosteroids in early ARDS secondary to septic shock was associated with better outcomes.[72] The DEXA-ARDS trial, the largest RCT on corticosteroids in early ARDS, demonstrated that dexamethasone (20 mg intravenous daily for 5 days, followed by 10 mg daily for 5 days) increased ventilator-free days on day 28 and reduced 60-day mortality.[73] A subsequent meta-analysis, including DEXA-ARDS data, confirmed a significant reduction in 30-day mortality,[74] supporting guideline recommendations for corticosteroid use in ARDS.[75]

In addition to corticosteroids, biologic agents targeting specific cytokines have shown promise. IL-1 receptor antagonism with anakinra improved respiratory function, reduced the need for mechanical ventilation, and lowered mortality in COVID-19-related ARDS, although these findings are limited by small sample sizes.[76]

IL-6 receptor blockade with tocilizumab, particularly when combined with dexamethasone, reduced TNF-α, IL-1β, IL-6, and IL-8 levels, and was associated with improved survival and reduced systemic inflammation in mechanically ventilated COVID-19 patients, despite an increased risk of secondary infections.[77–80]

Anti-TNFα therapies have demonstrated efficacy in preclinical models, with selective TNFR1 inhibition reducing VILI and improving lung function[81]; however, clinical trials in septic shock failed to show survival benefits.[82,83]

Other investigational agents, including IFN-γ inhibitors and JAK/STAT pathway blockers (e.g., ruxolitinib, baricitinib), remain under evaluation, with robust clinical data in ARDS still lacking.[84]

Emerging therapeutic strategies offer innovative approaches to “cytokine storm” mitigation. Cytokine nanosponges, composed of macrophage membrane-coated nanoparticles, scavenge circulating pro-inflammatory cytokines, reducing systemic inflammation and improving survival in preclinical sepsis models.[85]

Extracorporeal blood purification has been used to remove cytokines, with animal and early human studies showing reductions in IL-1β, IL-6, IL-8, and TNF-α.[86,87] However, in a randomized trial of patients with severe COVID-19-related ARDS on venovenous ECMO, early cytokine adsorption did not reduce IL-6 levels and was associated with decreased survival.[88] These findings highlight the need to identify patient subgroups, such as those with hyperinflammatory subphenotypes, who may derive the greatest benefit from extracorporeal therapies.

Mesenchymal stromal cells (MSCs) have been recognized for their potent immunomodulatory and trophic effects, rather than direct engraftment.[89] MSCs exert potent immunomodulatory effects by reprogramming key immune populations: they shift macrophages from a pro-inflammatory M1 to an anti-inflammatory M2 phenotype, modulate neutrophil activity, and induce regulatory T cells that secrete IL-10, transforming growth factor (TGF)-β, and other anti-inflammatory mediators.[90,91] By balancing pro- and anti-inflammatory signals, MSCs create a milieu conducive to tissue repair. Their paracrine factors and extracellular vesicles (EVs) restore alveolar–capillary barrier integrity, enhance alveolar fluid clearance, improve gas exchange, and promote antimicrobial defense.[92] Two placebo-controlled randomized trials showed that use of MSCs confirmed safety in diverse ARDS populations.[93,94] However, a recent phase 2b randomized trial reported no significant clinical benefit of MSC therapy in patients with moderate-to-severe ARDS, including those with COVID-19-associated disease.[95]

Limitations of live-cell therapy, such as variability in engraftment, survival, and scalability, have highlighted the therapeutic potential of MSC-derived extracellular vesicles (MSC-EVs). These vesicles encapsulate the bioactive factors responsible for MSC effects in a stable and controllable form, offering a next-generation, cell-free approach that preserves the immunomodulatory and reparative functions of MSCs.[96] Clinical studies demonstrate that MSC-EVs, administered either intravenously or via inhalation, are safe, biologically active, and capable of modulating inflammation and improving clinical parameters in moderate-to-severe ARDS.[97,98]

Nonetheless, these data remain preliminary, derived from small cohorts and heterogeneous study designs, and efficacy must be confirmed in larger, rigorously controlled trials. Major translational barriers, including standardization of EV production and characterization, development of potency assays, and determination of optimal dosing, also require resolution before clinical implementation is feasible.

Similarly, emerging cell-free immunomodulatory platforms such as cytokine nanosponges are in an early developmental stage. Although conceptually attractive, they currently lack robust clinical evidence, and promising preclinical data may not translate reliably to human ARDS. Their advancement is further limited by challenges related to manufacturing, *in vivo* stability, biodistribution, and regulatory requirements, all of which underscore the need for cautious interpretation of early results. Taken together, while these innovative strategies may eventually broaden precision, mechanism-directed therapeutic options for ARDS, their clinical readiness remains limited and warrants further rigorous translational and clinical investigation.

Controversies and unmet needs of clinical trials

A persistent challenge in evaluating therapeutic interventions in ARDS is the marked biological and clinical heterogeneity of the syndrome. ARDS represents a final common pathway of diverse insults—including sepsis, pneumonia, trauma, and viral infections – each eliciting distinct inflammatory and immune responses.[99] Even within the same etiology, patients may differ substantially in cytokine profiles, the extent of alveolar–capillary barrier disruption, and the timing and magnitude of immune dysregulation. This heterogeneity likely contributes to the inconsistency of clinical trial results, where therapies that show benefit in specific subgroups – such as corticosteroids, biologics, or MSC-based treatments – often fail to produce uniform benefit across unselected populations.

The timing of intervention further influences therapeutic efficacy. Immunomodulatory strategies may be effective when administered early to patients with a hyperinflammatory subphenotype, yet may be ineffective, or potentially harmful, when used in individuals with low-grade inflammation or in later phases of lung injury. Most clinical trials to date have not incorporated stratification based on biological profiles, limiting interpretation of results and increasing the likelihood that meaningful subgroup-specific effects remain undetected.

These considerations highlight the critical need for precision medicine approaches in ARDS. The identification and targeted treatment of biologically distinct subphenotypes, such as hyper-

inflammatory *vs.* hypoinflammatory ARDS, may enable more rational therapy selection and optimize the risk–benefit profile of interventions. Integrating biomarkers, transcriptomic and proteomic signatures, and functional immune assays into clinical trial design could support patient stratification and improve the accuracy of efficacy assessments.

In the long term, a precision medicine framework has the potential to shift ARDS management from primarily supportive care to individualized, disease-modifying strategies. Tailoring therapy to each patient's immunological and molecular profile may enhance control of cytokine-driven lung injury, reduce ventilator dependence, and ultimately improve survival. The field now faces the challenge of designing robust clinical studies that account for patient heterogeneity, validate predictive biomarkers, and evaluate interventions within well-defined subphenotypes, thereby establishing the foundation for a new era of targeted, biology-guided ARDS therapeutics.

Conclusions

Cytokine storm is a central driver of multiorgan dysfunction in ARDS, amplifying tissue injury and worsening patient outcomes. While current management remains largely supportive, including lung-protective ventilation and corticosteroid therapy, emerging interventions – such as targeted biologics, cytokine nanosponges, extracorporeal blood purification, as well as MSC and MSC-EV-based strategies – offer the potential to directly modulate the inflammatory cascade. The efficacy of these therapies may depend on patient-specific ARDS subphenotypes, particularly the hyperinflammatory group, highlighting the need for biomarker-guided, precision approaches. Integrating mechanistic insights with inflammatory profiling could enable individualized treatment, optimizing the timing, combination, and selection of immunomodulatory interventions. Advancing our understanding of the molecular pathways underlying "cytokine storm" will be critical to translating these novel therapies into clinical practice, ultimately mitigating organ injury, improving survival, and transforming ARDS care from primarily supportive to truly disease-modifying.

CRediT Authorship Contribution Statement

Raffaele Merola: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Patricia R.M. Rocco:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Investigation, Formal analysis. **Vito Marco Ranieri:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation. **Denise Battaglini:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Acknowledgments

None.

Funding

This research received no external funding. P.R.M.R. is supported by the Brazilian Council for Scientific and Technological Development (CNPq) (0306599/2023-6) and the Rio de Janeiro State Research Foundation (FAPERJ) (E-26/210.338/2022).

Ethics Statement

Not applicable.

Conflict of Interest

Given her role as Editorial Board Member, Denise Battaglini had no involvement in the peer-review of this article and has no access to information regarding its peer-review. Full responsibility for the editorial process for this article was delegated to another journal editor. The other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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